IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of
Muller et al.

Group Art Unit: 1618

U.S. App'n Ser. No.: 10/030,417

Examiner: Ebrahim, Nabila G.

Filed: 08/14/2002

Attorney Docket No: 668-59190

For: METHOD FOR CONTROLLED PRODUCTION OF ULTRAFINE MICROPARTICLES AND NANPARTICLES

* * * * *

15 September 2010

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the final rejection of claims 1-17, 20, 24-29, 31-34, and 38-47 of the subject application.

(i). Real Party in Interest:

This application is owned by Abbott GmbH & Co. KG.

(ii). Related Appeals and Interferences:

There are **no** other prior or pending appeals, interferences or judicial proceedings known to Appellant, the Appellant's legal representative, or assignee which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(iii). Status of Claims:

Claims 1-17, 20, 24-29, 31-34, and 38-47 are pending in this application.
Claims 1-17, 20, 24-29, 31-34, and 38-47 stand rejected.
The rejection of claims 1-17, 20, 24-29, 31-34, and 38-47 is appealed.
Please see the Claims Appendix for a copy of the claims under appeal.

(iv). Status of any Amendment Filed Subsequent to Final Rejection:

No amendments have been filed subsequent to final rejection.
A Notice of Appeal was filed on 16 June 2010 along with the appropriate fee.

(v). Summary of Claimed Subject Matter:

Independent claim 1 provides a process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number distribution, of 5.6 μm or less, the method comprising:

subjecting a matrix material comprising solid particles to a high-pressure homogenizing process in a piston-gap homogenizer in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water in which the solid particles are suspended and at temperatures of 20°C or less, which leads to a gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles. Basis for claim 1 can be found in the originally filed application, including at page 3, last paragraph to page 5, second paragraph, page 8, second paragraph to page 9, second paragraph, page 24, second to last paragraph, and page 25, last paragraph.

Independent claim 27 recites superfine micro- or nanoparticle dispersions having a particle size, as average diameter of the number distribution, of 5.6 μm or less, prepared according to a process comprising:

subjecting a matrix material to a high-pressure homogenizing process in a piston-gap homogenizer in an anhydrous or water-reduced medium containing less than 50 wt.% of water and/or at low temperatures of 20 °C or less, which leads to a gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material and forms a dispersion comprising the superfine micro- or nanoparticles. Basis for claim 27 can be found in the originally filed application, including at page 3, last paragraph to page 5, second paragraph, page 8, second paragraph to page 9, second paragraph, page 24, second to last paragraph, and page 25, last paragraph.

Independent claim 46 provides a process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number distribution, of 5.6 μm or less, the method comprising:

dispersing solid particles in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water to form a pre-suspension; and

subjecting the pre-suspension to a high-pressure homogenizing process in a piston-gap homogenizer to reduce the particle size without cavitation with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles. Basis for claim 46 can be found in the originally filed application, including at page 3, last paragraph to page 5, second paragraph, page 8, second paragraph to page 9, second paragraph, page 24, second to last paragraph, and page 25, last paragraph.

Independent claim 47 provides a process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number distribution, of 5.6 μm or less, the method comprising:

dispersing solid particles comprising a drug, pharmaceutical active ingredient, or veterinary drug in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water to form a pre-suspension; and

subjecting the pre-suspension to a high-pressure homogenizing process in a piston-gap homogenizer to reduce the particle size without cavitation with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles comprising the drug, pharmaceutical active ingredient, or veterinary drug. Basis for claim 47 can be found in the originally filed application, including at page 3, last paragraph to page 5, second paragraph, page 8, second paragraph to page 9, second paragraph, page 24, second to last paragraph, and page 25, last paragraph.

(vi). Grounds of Rejection to be Reviewed on Appeal:

A. Whether claims 1-17, 20, 24-29, 31-34 and 38-47 are patentable under 35 U.S.C. 103(a) over WO 98/14174 (Desai) in view of U.S. Patent No. 5,858,410 (Muller).

(vii). Argument:

A. **Claims 1-17, 20, 24-29, 31-34 and 38-47 are patentable under 35 U.S.C. 103(a) over WO 98/14174 (Desai) in view of U.S. Patent No. 5,858,410 (Muller).**

Claims 1-9, 15, 20, 25, 26, 28, 29, 31, 38, and 41-43 stand or fall together for purposes of this appeal only.

Claims 10-14, 32, 33, and 44 stand or fall together for purposes of this appeal only.

Claim 16 does not stand or fall with any other claim.

Claim 17 does not stand or fall with any other claim.

Claims 24, 39 and 40 stand or fall together for purposes of this appeal only.

Claims 27 and 45 does not stand or fall with any other claim.

Claim 34 does not stand or fall with any other claim.

Claims 46 and 47 stand or fall together for purposes of this appeal only.

The rejection of claims 1-17, 20, 24-26, 28, 29, 31-34, 38-44, 46 and 47 under 35 U.S.C. 103(a) as being unpatentable over WO 98/14174 (Desai) in view of U.S. Patent No. 5,858,410 (Muller) is respectfully traversed. The claimed invention is not obvious over the theoretical combination of Desai and Muller for the reasons of record and for the following reasons.

Appellant respectfully submits that the Examiner omitted essential elements of the claimed invention required for a prima facie rejection of claims 11-17, 20, 24-26, 28, 29, 31-34, 38-44, 46 and 47. Appellant respectfully submits that that the Examiner does not properly distinguish between:

1. Teachings in the prior art on how to produce the particles using a high pressure homogenization medium (also referred to as a dispersion medium); and
2. Teachings in the prior art on how to use the already produced particles in solvents, such as organic solvents.

Teachings on how to use the already produced particles are very different from teachings on how to produce the partcles in the first place and these teachings are not interchangeable.

The claimed invention requires the use of "an anhydrous or water-reduced dispersion medium containing less than 50 wt. % of water" as a high pressure homogenization medium in a piston-gap homogenizer to produce the particles. [See independent claims 1, 46 and 47.] The Examiner has not provided a prima facie case of obviousness since both Muller and Desai require the use of water in amounts greater than the claimed less than 50 wt.% as the dispersion medium. For this reason alone, the Section 103 rejection should be withdrawn.

Even if one of ordinary skill in the art did combine Desai and Muller, the claimed invention is not obvious over such a theoretical combination for the following reasons.

The present Appellant (Rainer Muller) is the Applicant in the cited Muller and, thus, Appellant is fully aware of the teachings of Muller. The entire specification of Muller requires the use of a large amount of water (about 80 to 99 % of water) as the dispersion medium in order to create cavitation and produce the particles. Muller teaches that the "dispersion principle is cavitation." See column 4, lines 6-7. Cavitation by definition requires a large amount water and, thus, Muller teaches against using less water. At column 5, lines 27-28, Muller teaches that "Suspensions were prepared with a drug, which was ground in an air jet, in an aqueous surfactant solution." [Emphasis added.] The specification of Muller in fact teaches that the high pressure dispersion medium is water or an aqueous medium containing about 80 to 99 % of water. There is no disclosure of using a non-aqueous dispersion medium or of a water reduced (less than about 50% of water) dispersion medium.

In some examples of Muller, glycerol is used as an emulsion stabilizer. However, glycerol cannot be considered as an organic solvent dispersion medium for high pressure homogenization, and even if it were, its content in all cases is below 16.7%. All other components used are solids (such as mannitol and phospholipon). Mannitol is introduced in form of an aqueous solution. Thus, there is no organic solvent at all in the dispersion medium.

Appellant respectfully submits that the Examiner's statement in the first paragraph of page 4 of the Final Office Action, in regards to claim 38 is incorrect. The disclosure of a feature of an active compound (drug) of being insoluble, only sparingly soluble or moderately soluble in organic solvents does not disclose that the organic solvents are used as the dispersion medium to produce the particles. Indeed, the Examiner has not, and cannot, cite any language in Muller that teaches to use less than 50 wt.% water in the dispersion medium to produce the particles.

Appellant respectfully submits that the Examiner misinterprets the Abstract of Muller at page 6, first paragraph of the Final Office Action, that "a step of further modifying a particle can still be considered as a method of producing a particle." The Abstract of Muller merely discloses that the drug carrier comprises particles of a pure

active compound, which is insoluble or sparingly soluble in organic solvents. This language absolutely does not teach or suggest that organic solvents, which contain less than 50 wt.% water, should be used as a dispersion medium in a piston-gap homogenizer. The Examiner has not, and cannot, cite any language in Muller that teaches to use less than 50 wt.% water in the dispersion medium. Dispersing particles produced by the water-based high pressure homogenization process of Muller thereafter in an organic solvent for further purposes cannot be read as a production of such particles in an organic solvent dispersion medium.

Desai does not provide the deficiencies of Muller. All of Desai's Examples use a dispersion medium of which 85% or more is water. This is by way of using a 1% (w/v) serum albumin solution in an amount resulting in such high water contents.

Appellant respectfully submits that the Examiner's assertion at the bottom of page 7 of the Final Office Action, that "Desai did not disclose the use of water in the process of making the particles in different embodiments (see for example 1) which teaches 30 mg paclitaxel disssolved in 3.0 ml human serum albumin soltion (1 % w/v)", has no factual basis. Example 1 of Desai on page 33 clearly discloses that 30 mg paclitaxel is dissolved in 3.0 ml of methylene chloride, which solution is added 27.0 ml of a solution of human serum albumin having a concentration of 1% w/v. This mixture is finally high pressure homogenized using an Avestin homogenizer. Thus, the major component of the dispersion medium is indeed water (90%). Moreover, the use of serum albumin as such is not the critical point. The critical point is that Desai uses it in form of a 1% w/v solution, and thus always introduces a high amount of water into the dispersion medium prior to the homogenization. These teachings in Desai cannot be ignored. The Examiner's statement at the top of page 9 of the Office Action that, "Further, the serum albumin as a solution is only disclosed in examples 22 and 23" is incorrect. A serum albumin solution is used in all examples of Desai. See e.g. Example 1 where it is stated that 27.0 ml of human serum albumin solution (1 % w/v) is added. A corresponding situation is explicitly mentioned in Desai's Examples 2, 4, 6, 7, 9, 10, 11, 12, 22, and 23.

Furthermore, Desai teaches away from using higher amounts of organic solvents. As can be seen from Example 7 of Desai at page 38, an alteration of the organic phase fraction showed that increasing the phase fraction led to a significant increase in particle size. Even a shift from 2% to 3% to 4% resulted in a particle size increase from 150 nm to 200 nm to 250 nm, which teaches to those skilled in the art that a further shift to an organic phase fraction of more than 50% would be expected to result in particle sizes well above the limit of the claimed invention. Thus, there is the clear teaching in Desai not to use dispersion media having a low (less than 85%) or even no water content.

It is general knowledge in the art to use water as dispersion medium for piston-gap homogenizers because only water has been considered to provide a sufficient amount of cavitation (Muller) effect required for piston-gap homogenizers to function. See page 4, last paragraph in the present specification. Consequently, use of a piston-gap homogenizer in anhydrous or considerably water reduced dispersion media (such as below 85% of water) was not known prior to the present invention. Thus, it is not a simple matter to change from one homogenizing device to another, such as from Desai's Avestin homogenizer to the claimed piston-gap homogenizer, without considering also the other requirements for such devices, in particular the homogenization medium.

Even if a person of ordinary skill in the art would have considered to use a piston-gap homogenizer with Desai's method, such a person would have seen the requirement to use mainly water as dispersion medium with an amount of 85% of water or higher, and therefore would not have considered with any expectance of success a reduction of the water content to below 50%. Thus, the combination of Desai and Muller would not have resulted in the claimed invention using an anhydrous or water-reduced (less than 50%) dispersion medium, but only in the use of a medium having a content of at least 85% of water. There is no disclosure in any of the cited documents which might invite a person of average skill in the art to modify their teachings in such a way that the presently claimed process would be obtained.

Regarding the Examiner's statement at the top of page 12 of the Final Office Action, it should be noted that the teachings of Muller with respect to cavitation and shear forces has to be divided. The cavitation effect is related to the use of a piston-gap homogenizer, while the shear and impact forces are related to other devices such a microfluidizer or nanojet using the jet stream principle. See column 4, lines 16-21, and column 5, lines 6-7, respectively. Since the claimed method requires the use of a piston-gap homogenizer, the mention of shear and impact forces related to other devices in Muller are of no relevance.

The primary goal of the present invention is to provide an effective yet gentle process for the preparation of hydrolysis and temperature sensitive micro- and nanoparticles, and stable dispersions thereof, with high chemical stability of active ingredients and increased dispersity of suspensions with prevented aggregation. See page 4, second paragraph in the present specification. The claimed invention allows the active ingredients to be filled into capsules without need for intermediate process steps of removal and addition of media, and to process the particles obtained to tablets and pellets. These goals are met by way of a unique and surprising combination of features:

- an anhydrous or considerably water reduced (less than 50% water) dispersion medium instead of mainly water, and in combination
- a piston-gap homogenizer instead of other homogenization devises such as a micro-fluidizer.

None of the prior art can realize these benefits since none teach or disclose the use of an anhydrous or considerably water reduced (less than 50% water) dispersion medium and the use of a piston-gap homogenizer.

In view of the many differences between the claimed invention and the theoretical combination of Desai and Muller, and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

A. **Claims 10-14, 32, 33, and 44 are separately patentable.**

Claims 10-14, 32, 33 and 44 are not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claims 10-14, 32, 33 and 44 all require that no water be present in the high pressure homogenization medium (dispersion medium) used in the piston-gap homogenizer. In contrast, the combination of Desai and Muller clearly require the use of large amounts of water in the dispersion medium, which is in a direction away from claims 10-14, 32, 33 and 44. For this reason alone, claims 10-14, 32, 33 and 44 are not obvious over the combination of Desai and Muller.

B. Claim 16 is separately patentable.

Claim 16 is not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claim 16 requires that less than 5 wt% water be present in the high pressure homogenization medium (dispersion medium) used in the piston-gap homogenizer. In contrast, the combination of Desai and Muller clearly require the use of far greater amounts of water in the dispersion medium, which is in a direction away from claim 16. For this reason alone, claim 16 is not obvious over the combination of Desai and Muller.

C. Claim 17 is separately patentable.

Claim 17 is not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claim 17 requires that less than 10 wt% water be present in the high pressure homogenization medium (dispersion medium) used in the piston-gap homogenizer. In contrast, the combination of Desai and Muller clearly require the use of far greater

amounts of water in the dispersion medium, which is in a direction away from claim 17. For this reason alone, claim 17 is not obvious over the combination of Desai and Muller.

D. Claim 34 is separately patentable.

Claim 34 is not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claim 34 requires that less than 1 wt% water be present in the high pressure homogenization medium (dispersion medium) used in the piston-gap homogenizer. In contrast, the combination of Desai and Muller clearly require the use of far greater amounts of water in the dispersion medium, which is in a direction away from claim 34. For this reason alone, claim 34 is not obvious over the combination of Desai and Muller.

E. Claims 46 and 47 separately patentable.

Claims 46 and 47 are not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claims 46 and 47 recite "subjecting the pre-suspension to a high-pressure homogenizing process in a piston-gap homogenizer to reduce the particle size **without cavitation** with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles."

As discussed above, the combination of Desai and Muller require the use of cavitation when using a piston-gap homogenizer. Thus, Desai and Muller teach in a direction away from the claimed invention. For this reason alone, the Section103 rejection should be withdrawn.

F. **Claims 24, 39 and 40 are separately patentable**.

Claims 24, 39 and 40 are not obvious over the combination of Desai and Muller for the many reasons provided above and for the following reasons.

Claims 24, 39 and 40 all require conducting the homogenization method at temperatures below the freezing point of water. The combination of Desai and Muller does not teach or suggest conducting homogenization at such low temperatures. Indeed, the claimed lower temperatures suppress the formation cavitation, which cavitation is required in the process of Muller. For this reason alone, claims 16 are not obvious over the combination of Desai and Muller.

G. Claims 27 and 45 are separately patentable.

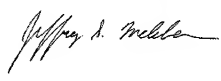
The rejection of claims 27 and 45 under 35 U.S.C. 103(a) as being unpatentable over WO 98/14174 (Desai) in view of U.S. Patent No. 5,858,410 (Muller) is respectfully traversed. The claimed invention is not obvious over the theoretical combination of Desai and Muller for the same reasons claim 1 is not obvious over Desai and Muller discussed above and for the following reasons.

Claims 27 and 45 recite particles produced by the process "which leads to a gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material and forms a dispersion comprising the superfine micro- or nanoparticles." Since the claimed particles are produced using the gentle homogenization, without the high shock waves of cavitation, less damage to the homogenized material is present compared to the particles produced using cavitation according to Muller. For this reason, claims 27 and 45 are not obvious over the combination of Desai and Muller.

Conclusion

In view of the lack of *prima facie* cases of obviousness, the many differences between the claimed invention and the cited references, and the unexpected advantages of the claimed invention, it is believed that this application clearly and patentably distinguishes over the combination of the cited references and is in proper condition for allowance. Accordingly, Appellants respectfully request that the Board allow claims 1-17, 20, 24-29, 31-34 and 38-47 over the cited reference.

Respectfully submitted,
Manelli Denison & Selter, PLLC



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(viii) Claims Appendix:

1. (Previously Presented) Process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number distribution, of 5.6 µm or less, the method comprising:

subjecting a matrix material comprising solid particles to a high-pressure homogenizing process in a piston-gap homogenizer in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water in which the solid particles are suspended and at temperatures of 20°C or less, which leads to a gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles.

2. (Previously Presented) Process according to claim 1, wherein the homogenized matrix material comprises at least one selected from the group consisting of drugs, pharmaceutical active ingredients, veterinary drugs, active ingredients, auxiliaries, additives for cosmetics, agricultural products, foodstuffs and preservatives.

3. (Previously Presented) Process according to claim 2, wherein the homogenized matrix material comprises at least one drug selected from the group consisting of ciclosporin, azodicarbonamide, paclitaxel, prednisolone, carbamazepine, taxol, morphine, diclofenac, ibuprofen, phenobarbital and cromoglycin.

4. (Previously Presented) Process according to claim 1, wherein the homogenized matrix material comprises at least one selected from the group consisting of synthetic, semi-synthetic or natural polymers, and natural macromolecules.

5. (Previously Presented) Process according to claim 4, wherein the homogenized matrix material comprises at least one selected from the group consisting of synthetic polymers, polylactide, polyglycolide, polylactide/-

glycolide co-polymer, polyorthoester, polyhydroxybutyrate (PHB), polyhydroxyvaleriate (PHV), polyhydroxybutyrate/-valeriate co-polymer, polyacryates, polymethacrylates, polyvinyl derivatives, block polymers of polyethylene glycol and polyesters, polyhydroxybutyric acid, polycyanoacrylates, polycarbonates and polycaprolacton.

6. (Previously Presented) Process according to claim 4, wherein the homogenized matrix material comprises at least one selected from the group consisting of natural macromolecules, alginates, albumin, serum albumin, human albumin, bovine albumin, collagen, casein, fibrin, tragacanth, xanthans, polysaccharides, chitin, dextrans and hyaluronic acid.

7. (Previously Presented) Process according to claim 1, wherein the homogenized matrix material comprises polymers or natural macromolecules loaded with drugs or active ingredients.

8. (Previously Presented) Process according to claim 7, wherein the homogenized matrix material comprises at least one polymer selected from the group consisting of polylactide, polyglycolide, polylactide/-glycolide co-polymer, polyorthoester, polyhydroxybutyrate (PHB), polyhydroxyvaleriate (PHV), and polyhydroxybutyrate/-valeriate co-polymer.

9. (Previously Presented) Process according to claim 7, wherein the homogenized matrix material comprises at least one selected from the group consisting of natural macromolecules, in particular alginates, albumin, preferably serum albumin, human albumin and bovine albumin, collagen, casein, fibrin, bentonite, tragacanth, xanthans, polysaccharides such as chitin, dextrans and hyaluronic acid.

10. (Previously Presented) Process according to claim 1, wherein the materials to be reduced in size are dispersed in a non-aqueous dispersion medium.

11. (Previously Presented) Process according to claim 10, wherein the materials to be reduced are dispersed in an oily medium.

12. (Previously Presented) Process according to claim 10, wherein the materials to be reduced are dispersed in liquid hydrocarbons.

13. (Previously Presented) Process according to claim 10, wherein the materials to be reduced are dispersed in at least one selected from the group consisting of polyethylene glycols (PEGs), PEG 100 to PEG 1000, anhydrous glycerol, anhydrous alcohols, methanol, ethanol, 1-propanol, isopropanol, n-butanol, 2-butanol, pentanol, hexanol, octanol, decanol, allyl alcohol, propargyl alcohol, ethanol, isopropanol butanol, and propylene glycols.

14. (Previously Presented) Process according to claim 10, characterized in that the materials to be reduced are dispersed in dimethyl sulfoxide.

15. (Previously Presented) Process according to claim 1, wherein the materials to be reduced are dispersed in a dispersion medium that contains a small or minimized proportion or proportion desired, for product-related reasons, of water.

16. (Previously Presented) Process according to claim 15, wherein the materials to be reduced are dispersed in a dispersion medium containing less than 5 wt.-% water.

17. (Previously Presented) Process according to claim 15, wherein the materials to be reduced are dispersed in a dispersion medium which contains less than 10 wt.-% water.

18. (Cancelled)

19. (Cancelled)

20. (Previously Presented) Process according to claim 15, wherein the materials to be reduced are dispersed in a dispersion medium comprising water and at least one dissolved substance selected from the group consisting of polymers, polyethylene glycols solid at room temperature, PEG 6000, cellulose derivatives, and hydroxypropyl methylcellulose (HPMC).

21. (Cancelled)

22. (Cancelled)

23. (Cancelled)

24. (Previously Presented) Process according to claim 1, wherein the process temperature is below the freezing point of water.

25. (Previously Presented) Process according to claim 1, wherein the process is carried out with the exclusion of oxygen.

26. (Previously Presented) Process according to claim 1, further comprising degassing the dispersion medium before use.

27. (Previously Presented) Superfine micro- or nanoparticle dispersions having a particle size, as average diameter of the number distribution, of 5.6 µm or less, prepared according to a process comprising:

subjecting a matrix material to a high-pressure homogenizing process in a piston-gap homogenizer in an anhydrous or water-reduced medium containing less than 50 wt.% of water and/or at low temperatures of 20 °C or less, which leads to a gentle particle size reduction with minimization of the impairment of the chemical stability of the homogenized material and forms a dispersion comprising the superfine micro- or nanoparticles.

28. (Previously Presented) Process according to claim 1, wherein the particle size is less than 5 µm.

29. (Previously Presented) Process according to claim 1, wherein the particle size is less than 1 µm.

30. (Cancelled)

31. (Previously Presented) Process according to claim 1, wherein the homogenization process is conducted at temperatures below the freezing point of water.

32. (Previously Presented) Process according to claim 11, wherein the oily medium comprises at least one selected from the group consisting of medium chain triglycerides (MCT), peanut oil, avocado oil, cottonseed oil, safflower oil, long chain triglycerides (LCT), in particular soybean oil, triacetin and isopropyl myristate.

33. (Previously Presented) Process according to claim 12, wherein the liquid hydrocarbon comprises at least one selected from the group consisting of fluid paraffin, viscous paraffin, hexane and octane.

34. (Previously Presented) Process according to claim 16, wherein the dispersion medium contains less than 1 wt.-% of water.

Claims 35-37 (Cancelled)

38. (Previously Presented) Process according to claim 1, wherein the process temperature is 4°C.

39. (Previously Presented) Process according to claim 24, wherein the process temperature is below -20°C.

40. (Previously Presented) Process according to claim 24, wherein the process temperature is below -50°C.

41. (Previously Presented) Process according to claim 25, further comprising gassing the matrix material and medium with inert gases.

42. (Previously Presented) Process according to claim 41, wherein the inert gas comprises at least one selected from the group consisting of nitrogen and argon.

43. (Previously Presented) Process according to claim 25, wherein the homogenization process is conducted under a vacuum.

44. (Previously Presented) Process according to claim 1, wherein the homogenizing process is conducted in a piston-gap homogenizer in an anhydrous medium.

45. (Previously Presented) Process according to claim 27, wherein the homogenizing process is conducted in a piston-gap homogenizer in an anhydrous medium.

46. (Previously Presented) Process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number

distribution, of 5.6 μm or less, the method comprising:

dispersing solid particles in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water to form a pre-suspension; and

subjecting the pre-suspension to a high-pressure homogenizing process in a piston-gap homogenizer to reduce the particle size without cavitation with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles.

47. (Previously Presented) Process for the gentle preparation of superfine micro- and nanoparticles having a particle size, as average diameter of the number distribution, of 5.6 μm or less, the method comprising:

dispersing solid particles comprising a drug, pharmaceutical active ingredient, or veterinary drug in an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water to form a pre-suspension; and

subjecting the pre-suspension to a high-pressure homogenizing process in a piston-gap homogenizer to reduce the particle size without cavitation with minimization of the impairment of the chemical stability of the homogenized material, to form superfine micro- and nanoparticles comprising the drug, pharmaceutical active ingredient, or veterinary drug.

(ix) Evidence Appendix:

Not applicable.

(x) Related Proceedings Appendix:

Not applicable.